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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,347	SEIBLER ET AL.	
	Examiner	Art Unit	
	MARCIA S. NOBLE	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-40,45,47 and 48* is/are pending in the application.

4a) Of the above claim(s) *14-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Withdrawn Rejections/Objections

The rejection of claims 45 and 47, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn. Applicant amended claim 45 and 47 to recites, "said short hairpin RNA construct", which now has proper antecedent basis. Applicant also amended claim 47 to remove the recitation of "mouse" and replaced it with "tissue or cell culture", which clarifies the claim.

The following rejection of record has been modified to address the amendments to the claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45, 47, and 48, as amended, are rejected under 35 U.S.C. 103(a) as obvious over Lowe (Lowe et al. US 2008/0226553 A1; Pub Date:9/18/2008; effective filing date:9/27/2002) in further view of Beach (US 2004/0086884 effective filing date:3/16/2000).

The amended claims are more narrowly drawn to a transgenic mouse or in vitro tissue/cells comprising an expression vector stably integrated into a polymerase II

depended locus by site specific integration, said vector comprising a short hairpin RNA operably linked to a polymerase III dependent promoter and sequences suitable for targeted integration at the polymerase II dependent locus. The claims are also drawn to said expression vector. The new limitations require the short hairpin RNA to be operably linked to a polymerase II dependent promoter instead of a ubiquitous promoter as previously claims.

Lowe teaches an expression vector encoding a firefly luciferase shRNA construct flanked by two targeting sequences that target integration of the expression vector to the polymerase II dependent, *hprt* gene locus of a mouse genome. Upon recombination and integration of the expression vector into the *hprt* gene locus, the luciferase shRNA construct is operably linked to the ubiquitous mouse *hprt* promoter (Figure 23). Thus, the shRNA construct is under control of a ubiquitous promoter as claimed. Lowe teaches that this expression vector is intended for introduction into mouse embryonic stem (ES) cells (p. 17, par [0172], line 1 to par [0173], line 9).

Lowe teaches introducing the luciferase shRNA expression vector, discussed above, into cultured mouse ES cells comprising and expressing a firefly luciferase gene. Lowe further teaches that said introduction of the luciferase shRNA expression vector results in high levels of site specific integration of the expression vector into the *hprt* gene of the mouse ES cells (p. 17, par [0173], lines 1-9). Lowe teaches that expression of the luciferase shRNA expression construct by the mouse ES cells effectively suppressed firefly luciferase activity in the ES cells (p. 17, [0174], lines 1-10). The preamble of claim 47 recites a tissue or cell culture "obtained from a mouse". The

breadth of this recitation encompasses a product-by-process claim that encompasses a tissue or cell product produced by the process of isolating tissues or cells from a mouse that harbors the claimed shRNA expression construct. While Lowe obtains the ES cell culture harboring the claimed expression vector by a different process (i.e.-directly introducing the expression vector into cultured ES cells), the ES cells disclosed by Lowe are structurally indistinguishable from the cells encompassed by the claims. Therefore, the recitation, "obtained from a mouse" in this instant does not impart patentable weight because the structural limitations of the claimed cell culture or tissue has been disclosed by Lowe. Therefore, Lowe teaches the claimed cell culture.

Lowe teaches that the shRNA expression construct and ES cells comprising the shRNA expression construct, as discussed above, are part of a system for creating genetically defined RNAi "epi-alleles" in mice using Cre-mediated recombination to stably integrate a single RNAi expression cassette into a single locus in the mouse genome. Lowe teaches that this technique will minimize clonal variation due to random integration events. Lowe teaches that the system was developed to mediate the integration of a single shRNA expression cassette into mouse ES cells. Lowe teaches the system relies upon the ability to integrate a "donor plasmid" containing a shRNA expression construct, into an “acceptor” locus through transient expression of Cre recombinase. Lowe teaches that this system is designed so that proper recombinants can be selected through reconstitution of the *hprt* gene. Lowe further teaches additionally, both the donor and acceptor constructs express coat color gene markers which can be used to score chimeric mice (p. 17, par [0172], lines 1-20). Lowe does not

explicitly teach a mouse comprising the shRNA luciferase/hprt expression vector with a luciferase repression phenotype. However, Lowe does teach the ES cell harboring and expressing the luciferase shRNA have suppressed luciferase expression and suggests that the ES cells are intended for producing mice with shRNA suppression of targeted genes. Although Lowe does not make the mouse, the mouse is clearly contemplated and it was well within the skill of the ordinary artisan at the time of filing to make the mouse envisioned and discussed by Lowe. Therefore, from the teachings of Lowe, an artisan of ordinary skill at the time of the invention would be able to produce a mouse comprising an expression vector comprising a shRNA construct that integrates into a polymerase II dependent locus and results in suppression of expression of a gene targeted by said shRNA with a reason expectation of success. Also, since an artisan of ordinary skill would have a reasonable expectation of obtaining the claimed mouse from the teachings of Lowe, an artisan would also be able to obtain tissues and cells from said mouse as is encompassed by claim 47.

In this particular example, Lowe does not teach the newly added limitations that the short hairpin RNA is operably linked to a polymerase III-dependent promoter. However, Lowe does teach that in the short hairpin RNA expression construct polymerase III promoters, such as the U6 promoter, are desirable for directing expression of the short hairpin RNA because such promoters are known to produce efficient silencing (p. 5, [0067], lines 5-7).

Further, Beach teaches that in their in vivo use of luciferase short hairpin RNA expression constructs operably linked to polymerase II promoters, they had reduced

efficiency of the short hairpins RNA transcription. Beach improved efficiency and switched to an polymerase III dependent promoter, such as U6 or H1, which Beach teaches are well defined and well studied promoters (p. 28, [0301], line 1 to p. 29, [302], last line). Thus, an ordinary artisan would impart for the teachings of Beach that a polymerase III dependent promoter to drive expression of a short hairpin RNA would be preferable to a polymerase II dependent promoter because the polymerase III dependent promoter more effectively drives expression of short hairpin RNAs than the polymerase II dependent promoter.

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. 389, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some

teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

In the present situation, rationales A, B, E, F and G are applicable. It would have been obvious to an artisan of ordinary skill at the time the inventions was made to make a variant of the expression vector, cells, and mouse, taught by Lowe, by incorporating a polymerase III dependent promoter into the luciferase short hairpin RNA expression construct, taught by Lowe, to drive expression of the short hairpin RNA, as opposed to relying on the endogenous mouse polymerase II dependent promoter, hprt promoter, to drive the short hairpin RNA, using molecular biology methods well established in the art to predictably produce the mouse, cells, and expression vector of the amended claims with a reasonable expectations of success. Further an artisan would be motivated to incorporate a RNA polymerase III dependent promoter, such as U6 or H1 promoter, because Lowe teaches that RNA polymerase III dependent promoters predictably result in highly efficient silencing and Beach teaches that RNA polymerase III dependent promoters are more effective in short hairpin RNA production than the RNA polymerase II dependent promoters.

Thus, the teachings of the cited prior art in the obviousness rejection above provide the requisite teachings and motivations with a clear, reasonable expectation. The cited prior art meets the criteria set forth in both Graham and KSR.

Response to Arguments

Applicant's arguments filed 3/1/2010 have been fully considered but they are not persuasive. Applicant assert that rejection relies upon the use of the endogenous mouse polymerase II dependent promoter, hprt, when integrated into the genome. Applicant states that the claims now require the use of a polymerase dependent promoter to drive expression of the short hairpin RNA sequence. Applicant asserts that Lowe does not suggest the combination of a polymerase II dependent locus with a heterologous polymerase III dependent promoter with a reasonable expectation of success. Applicant asserts that a person of ordinary skill in the art would not have had a reasonable expectation that such a combination would provide a successful and effective expression of shRNA.

Applicant's argument is not found persuasive. Contrary to Applicant's assertion, Lowe does teach the combinations of a polymerase II dependent locus and a heterologous polymerase III promoter with a reasonable expectation of success. While, Lowe does not teach this combination explicitly, Lowe does teach expression vectors comprising polymerase III dependent promoters operably linked to shRNAs. Lowe also teaches targeted integration into a polymerase II dependent locus using hprt flanking sequences around the shRNA construct. Lowe further teaches that polymerase III dependent promoters are efficient and effective promoters to drive silencing of a target gene by shRNA. Therefore, in and of itself, Lowe does teach all the components of the claims expression vector, cells, and mouse and additionally provides a motivation to produce a variant wherein the shRNA construct has its own promoter, specifically an

RNA polymerase III dependent promoter. Additionally, Beach was added to demonstrate the specific teaching of a motivation to use a polymerase III-dependent promoter. Beach teaches that such promoters would improve sRNA expression and thus silencing. Therefore, the prior art provides strong motivation to add an RNA polymerase III dependent promoter to the shRNA expression construct of Lowe. Applicant suggests that this is no reasonable expectation of success in such combinations. Examiner does not agree because targeted insertion, integration, and expression of an expression vector was successful and predictable in the prior art, as demonstrated by Lowe. Further, shRNA expression constructs comprising polymerase III dependent promoters, such as U6 promoter, operably linked to shRNA sequences were well established and predictable in the prior art, as demonstrated by Lowe and Beach. Therefore, in combination these two elements would have a reasonable expectation of success because the targeted insertion of expression vectors and the expression of shRNA driven by a polymerase III dependent promoter are both well-established and predictable. Further there is no reason to believe the addition of the polymerase III dependent promoter into the expression vector of Lowe would not work. The addition of the polymerase III dependent promoter solely disconnects the control of expression from the hprt gene and would allow for successful independent expression of both the reconstituted hprt gene and the luciferase shRNA. Further, as discussed above the use of targeted integration will minimize clonal variation due to random integration events, as taught by Lowe, therefore, providing addition reasoning to combine the teachings. Therefore, contrary to Applicant's assertion, the combination of

the teachings of Lowe are fully compatible and would have a reasonable expectation of success. Thus, because Lowe, in view of Beach, teaches the amended claims and Applicant's arguments are not persuasive in overcoming the art, the instant claims remained rejected.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCIA S. NOBLE whose telephone number is (571)272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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